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☐ 21: Trends Endocrinol Metab 1999 Aug;10(6):216-222

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TGF-beta Family Members and Gonadal Development.

Josso N, di Clemente N.

Unite de Recherches sur l'Endocrinologie du Developpement (INSERM), E
 Superieure, Departement de Biologie, 1 rue Maurice-Arnoux, 92120 Montr

Several members of the transforming growth factor beta (TGF-beta) family in gonadal development; namely, TGF-beta itself, inhibins, activins, anti-M hormone (AMH) and GDF-9. These proteins do not affect initial gonadal or but play either a stimulatory or inhibitory role in the division and differentiation of gonadal cells and in meiotic maturation in the female. Furthermore, as shown by transgenic mouse technology, both AMH and inhibin act as tumor suppressors.

PMID: 10407395 [PubMed - as supplied by publisher]

☐ 22: Cell Tissue Res 1999 Jul;297(1):103-10

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Expression of a novel member of the TGF-beta superfamily, growth/differentiation factor-15/macrophage-inhibiting cytokine 15/MIC-1) in adult rat tissues.

Bottner M, Suter-Crazzolara C, Schober A, Unsicker K.

Department of Neuroanatomy, University of Heidelberg, Im Neuenheimer Feld 69120 Heidelberg, Germany.

We have cloned a novel member of the transforming growth factor-beta (TGF-beta) superfamily from a human placental cDNA library. The sequence is identical to recently published sequences, of which only one (macrophage inhibitory cytokine 15/MIC-1) has been characterized in terms of function. In light of the present c

demonstrating the wide distribution of the mRNA and putative multifunctional growth/differentiation factor-15/MIC-1 (GDF-15/MIC-1). The deduced amino acid sequence reveals typical features of a secreted molecule. The choroid plexus of the choroid plexus is the only site in the adult brain expressing levels of GDF-15/MIC-1 mRNA. Many epithelia of non-neural tissues including the prostate and intestinal mucosa, bronchi and bronchioli, secretory tubuli of the submandibular gland, and lactating mammary gland are prominent sites of GDF-15/MIC-1 synthesis. GDF-15/MIC-1 is also strongly expressed by macrophages in the spleen. Thus, GDF-15/MIC-1, like many other members of the TGF-beta superfamily, is widely distributed in adult tissues, being most strongly expressed in epithelial cells and macrophages.

PMID: 10398887 [PubMed - indexed for MEDLINE]

23: Mol Endocrinol 1999 Jun;13(6):1035-48

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Paracrine actions of growth differentiation factor-9 in the mouse ovary.

Elvin JA, Clark AT, Wang P, Wolfman NM, Matzuk MM.

Department of Pathology, Baylor College of Medicine, Houston, Texas 77030

Although the transforming growth factor-beta (TGF-beta) superfamily is the largest family of secreted growth factors, surprisingly few downstream target genes and signaling pathways have been identified. Likewise, the identities of oocyte-secreted factors, which regulate important oocyte-somatic cell interactions, are largely unknown. For example, oocytes are known to secrete paracrine growth factors which are necessary for cumulus expansion, induction of hyaluronan synthesis, and suppression of LH receptor (LHR) mRNA synthesis. Our previous studies showed that absence of the TGF-beta family member, growth differentiation factor-9 (GDF-9), blocks ovarian folliculogenesis at the primary follicle stage leading to infertility. In the present study, we demonstrate that mouse GDF-9 protein is expressed in all stages of folliculogenesis beginning at the type 3a follicle stage including antral follicles. To explore the functions of GDF-9 in the later stages of folliculogenesis and cumulus expansion, we produced mature, glycosylated, recombinant mouse GDF-9 using a Chinese hamster ovary cell expression system. A granulosa cell culture system was established to determine the role of GDF-9 in the regulation of several key ovarian genes by semiquantitative RT-PCR. We find that recombinant GDF-9 induces hyaluronan synthase 2 (HAS2), cyclooxygenase 2 (COX-2), and steroidogenic acute regulatory protein (StAR) mRNA synthesis but suppresses urokinase plasminogen activator (uPA) and LHR mRNA synthesis. Consistent with the induction of StAR mRNA, recombinant GDF-9 increases granulosa cell progesterone synthesis in the presence of FSH. Since induction of HAS2 and suppression of the protease uPA are key events in the production of the hyaluronan-rich extracellular matrix produced during cumulus expansion, we determined whether GDF-9 could regulate this process. Using oocyctomized cumulus cell-oocyte complexes, we show that

recombinant GDF-9 induces cumulus expansion in vitro. These studies demonstrate that GDF-9 can bind to receptors on granulosa cells to regulate the expression of gene products. Thus, in addition to playing a critical function as a growth and differentiation factor during early folliculogenesis, GDF-9 functions as an oocyte-secreted paracrine factor to regulate several key granulosa cell enzymes involved in cumulus expansion and maintenance of an optimal oocyte microenvironment, which are essential for normal ovulation, fertilization, and female reproduction.

PMID: 10379900 [PubMed - indexed for MEDLINE]

☐ 24: J Neurosci Res 1999 Jun 1;56(5):482-92

Related Articles



Localized expression of BMP and GDF mRNA in the rodent brain

Soderstrom S, Ebendal T.

Department of Neuroscience, Biomedical Center, Uppsala University, Sweden

Expression of BMP- and GDF-related factors within the transforming growth factor (TGF-beta) superfamily was examined in the rat and mouse brain by in situ hybridization. Strong signals were obtained in neurons for GDF-1 and GDF-10. GDF-1 is expressed at postnatal day 6 in the cerebral cortex, hippocampal CA1 through CA3 neurons, while only weakly expressed by cells in the dentate gyrus. Granule neurons in the polymorph layer of the dentate gyrus are GDF-1-positive, as are the majority of neurons in the cortex. GDF-10 shows a distinct pattern of expression with strong labelling was seen in the superficial layers of cortex, notably in the prefrontal and cingulate cortex, and in CA3 and dentate gyrus. From postnatal day 21, GDF-10 expression is strong in the hippocampus, cortex, and thalamic nuclei, while GDF-1 expression becomes restricted to the granule cell layer in the dentate gyrus. OP-1 expression is restricted throughout development to cells of the medial septal nucleus, choroid plexus, and leptomeninges. The markedly different expression patterns of these BMPs suggest they serve separate functions in the brain.

PMID: 10369215 [PubMed - indexed for MEDLINE]

☐ 25: J Cell Physiol 1999 Jul;180(1):1-9

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Myostatin, a transforming growth factor-beta superfamily member, is expressed in heart muscle and is upregulated in cardiomyocyte infarct.

Sharma M, Kambadur R, Matthews KG, Somers WG, Devlin GP, Conboy PJ, Bass JJ.

Growth Physiology, AgResearch, Ruakura, Hamilton, New Zealand.
SharmaM@agresearch.cri.nz

Myostatin is a secreted growth and differentiating factor (GDF-8) that belongs to the transforming growth factor-beta (TGF-beta) superfamily. Targeted disruption of the myostatin gene in mice and a mutation in the third exon of the myostatin gene in muscled Belgian Blue cattle breed result in skeletal muscle hyperplasia. Here, myostatin has been shown to be involved in the regulation of skeletal muscle in both mice and cattle. Previous published reports utilizing Northern hybridization have shown that myostatin expression was seen exclusively in skeletal muscle. A lower level of myostatin mRNA was also reported in adipose tissue. Using a reverse transcription-polymerase chain reaction (RT-PCR) technique and Western blotting with anti-myostatin antibodies, we show that myostatin mRNA is not restricted to skeletal muscle. We also show that myostatin expression is present in the muscle of both fetal and adult hearts. Sequence analysis reveals that the heart myostatin cDNA sequence contains an 11 nucleotide deletion in the third exon that causes a frameshift that eliminates virtually all of the mature, active region of the protein. Anti-myostatin immunostaining on heart sections also demonstrates that myostatin protein is localized in Purkinje fibers and cardiomyocytes in heart tissue. Following myocardial infarction, myostatin expression is upregulated in the cardiomyocytes surrounding the infarct area. Given that myostatin is expressed in fetal and adult hearts and that myostatin expression is upregulated in cardiomyocytes following myocardial infarction, myostatin could play an important role in cardiac development and physiology.

PMID: 10362012 [PubMed - indexed for MEDLINE]

☐ 26: Biochem Biophys Res Commun 1999 Mar 16;256(2):419-24 Related Articles



Bone morphogenetic protein-3b (BMP-3b) gene expression is correlated with differentiation in rat calvarial osteoblasts.

Hino J, Matsuo H, Kangawa K.

National Cardiovascular Center Research Institute, Osaka, Fujishirodai, Suita, Japan.

BMP-3b (also called GDF-10) is a novel BMP-3-related protein recently discovered in rat femur tissue. Gene expression of BMP-3b in osteoblastic cells and its regulation during prolonged culture, BMP-2 and transforming growth factor beta1 (TGF-beta1) treatment were examined. The BMP-3b gene was highly expressed in rat osteoblasts obtained from calvarial bones but not in the osteoblastic cell lines (MC3T3-E1 and U2-OS). BMP-3b mRNA increased during osteoblastic differentiation in prolonged culture and was associated with increased alkaline phosphatase (ALPase) activity. When BMP-3b enhancer of ALPase activity, was added to the primary osteoblast culture, BMP-3b mRNA increased 6.9-fold after 24 h. In contrast, TGF-beta1 treatment, which increased ALPase activity, rapidly and completely inhibited gene expression of BMP-3b.

regulation of BMP-3 mRNA differed from that of BMP-3b, even though bo share 81% identity. These findings indicate that BMP-3b gene expression is osteoblastic differentiation and BMP-3b functions in highly differentiated o
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PMID: 10079200 [PubMed - indexed for MEDLINE]

☐ 27: Genome Res 1999 Feb;9(2):121-9

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**Isolation of zebrafish *gdf7* and comparative genetic mapping o
belonging to the growth/differentiation factor 5, 6, 7 subgroup
TGF-beta superfamily.**

**Davidson AJ, Postlethwait JH, Yan YL, Beier DR, van Doren C, Foern
Celeste AJ, Crosier KE, Crosier PS.**

Department of Molecular Medicine, School of Medicine, University of Auc
Auckland, New Zealand.

The Growth/differentiation factor (Gdf) 5, 6, 7 genes form a closely related belonging to the TGF-beta superfamily. In zebrafish, there are three genes t the Gdf5, 6, 7 subgroup that have been named radar, dynamo, and contact. radar and dynamo both encode proteins most similar to mouse GDF6. The c identity of these genes on the basis of amino acid similarities has not been c have identified *gdf7*, a fourth zebrafish gene belonging to the Gdf5, 6, 7 sub assign correct orthologies and to investigate the evolutionary relationships c mouse, and zebrafish Gdf5, 6, 7 subgroup, we have compared genetic map the zebrafish and mammalian genes. We have mapped zebrafish *gdf7* to lin (LG) 17, contact to LG9, GDF6 to human chromosome (Hsa) 8 and GDF7 t radar and dynamo genes have been localized previously to LG16 and LG19. A comparison of syntenies shared among human, mouse, and zebrafish gen indicates that *gdf7* is the ortholog of mammalian GDF7/Gdf7. LG16 shares relationships with mouse chromosome (Mmu) 4, including Gdf6. Portions c LG19 appear to be duplicate chromosomes, thus suggesting that radar and c both orthologs of Gdf6. Finally, the mapping data is consistent with contact zebrafish ortholog of mammalian GDF5/Gdf5.

PMID: 10022976 [PubMed - indexed for MEDLINE]

☐ 28: Development 1999 Mar;126(6):1305-15

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Mechanisms of GDF-5 action during skeletal development.

Francis-West PH, Abdelfattah A, Chen P, Allen C, Parish J, Ladher R, MacPherson S, Luyten FP, Archer CW.

Department of Craniofacial Development, Guy's, King's and St Thomas' School of Dentistry, Guy's Tower, Floor 28, London Bridge, London, SE1 9RT, UK.
pfrancis@hgmrc.mrc.ac.uk

Mutations in GDF-5, a member of the TGF-beta superfamily, result in the recessive syndromes brachypod (bp) in mice and Hunter-Thompson and Gracilis chondrodysplasias in humans. These syndromes are all characterised by the the appendicular skeleton and loss or abnormal development of some joints. To investigate how GDF-5 controls skeletogenesis, we overexpressed GDF-5 in limb development using the retrovirus, RCASBP. This resulted in up to a 30% increase in length of the skeletal elements, which was predominantly due to an increase in number of chondrocytes. By injecting virus at different stages of development we show that GDF-5 can increase both the size of the early cartilage condensation and the size of a developing skeletal element. Using in vitro micromass cultures as a model to study the early steps of chondrogenesis, we show that GDF-5 increases chondrocyte proliferation in a dose-dependent manner. We did not detect changes in proliferation. However, suspension cultures showed that GDF-5 might act at these stages by increasing cell-cell adhesion, a critical determinant of early chondrogenesis. In contrast, pulse labelling experiments of GDF-5-infected limbs showed that at later stages of skeletal development GDF-5 can increase proliferation of chondrocytes. Thus, here we show two different ways of how GDF-5 may control different stages of skeletogenesis. Finally, our data show that levels of GDF-5 expression/activity are important in controlling the size of skeletal elements and provides a possible explanation for the variation in the severity of defects resulting from mutations in GDF-5.

PMID: 10021348 [PubMed - indexed for MEDLINE]

☐ 29: Invest Ophthalmol Vis Sci 1999 Feb;40(2):296-311

Relate

Bone morphogenetic proteins and growth and differentiation of the human cornea.

You L, Kruse FE, Pohl J, Volcker HE.

Department of Ophthalmology, University of Heidelberg Medical School, C

PURPOSE: To investigate transcription of members of the transforming growth factor (TGF)-beta superfamily and corresponding receptors in human corneal epithelium and stroma. **METHODS:** Transcription of bone morphogenetic proteins (BMP)-2, BMP-4, BMP-5, and BMP-7; growth-differentiation factor (GDF)-5, and BMP type I receptors (BMPRI) types I (BMPRI-IA, BMPRI-IB) and II (BMPRII) was investigated by reverse transcription-polymerase chain reaction (RT-PCR) in ex vivo and corneal cultures. For verification, PCR fragments were cloned and sequenced. DNA dot blot

performed to estimate the level of transcription. RNA dot blots were performed to determine expression of GDF-5. Expression of BMP receptor proteins was determined by immunohistochemistry. Single-cell clonal growth proliferation assays were performed using recombinant human GDF-5 and TGF-beta1. RESULTS: Transcription of BMP-3, BMP-4, BMP-5, and BMP-7 and receptors of BMPR-IA, BMPR-II was detected in ex vivo and cultured epithelium and stroma. The level of expression was higher in cultured stroma for all factors, but the level for the receptors was higher in cultured epithelium. In contrast GDF-5 was transcribed only in stromal cells, suggesting that this cytokine may be an important mediator between keratocytes and epithelium. Furthermore, GDF-5 inhibited proliferation of corneal epithelial and stromal cells. CONCLUSIONS: Given the importance of the TGF-beta family during embryonic development, the results suggest that its members may be components of the cytokine network and may participate in the regulation of cellular proliferation and differentiation.

PMID: 9950587 [PubMed - indexed for MEDLINE]

□ 30: Mech Dev 1998 Nov;78(1-2):135-40

Related Articles, Nucleotide, Protein

A novel growth differentiation factor-9 (GDF-9) related factor expressed with GDF-9 in mouse oocytes during folliculogenesis

Laitinen M, Vuojolainen K, Jaatinen R, Ketola I, Aaltonen J, Lehtonen Heikinheimo M, Ritvos O.

Department of Bacteriology and Immunology, Haartman Institute, P.O. Box 56, University of Helsinki, FIN-00014, Helsinki, Finland. mplaletin@cc.helsinki.fi

Growth differentiation factor-9 (GDF-9) is a transforming growth factor-beta family member which is expressed in the oocytes in mouse ovaries (McGrath et al., 1995). Oocyte-specific expression of growth/differentiation factor-9. Mol. Endocrinol. 9, 131-136). GDF-9 is indispensable for normal folliculogenesis since female mice deficient for the GDF-9 gene are infertile due to arrest of follicular growth at the primary follicle stage (Dong, J., Albertini, D., Nishimori, K., Kumar, T.R., Lu, N., Matzuk, M.M., 1996. Growth differentiation factor-9 is required during early ovarian folliculogenesis. Nature 383, 531-535). We searched the GenBank Expressed Sequence Tag (EST) database with the mouse GDF-9 sequence, and identified from a mouse 2-cell embryo library an EST cDNA that encodes a putative member of the TGF-beta superfamily, and named it as GDF-9B. No hybridization analyses of mouse ovaries revealed a single transcript of approximately 2.0 kb for GDF-9B and of 2.0 kb for GDF-9. We cloned by reverse transcription-polymerase chain reaction from mouse ovarian RNA a partial 821-base pair cDNA that spans the sequence encoding the putative mature region of GDF-9. The COOH-terminal region of GDF-9B appears to be 53% homologous to GDF-9. Unlike GDF-9, GDF-9B lacks the cysteine residue needed for the covalent dimerization of several TGF-beta family members. Using in situ hybridization analysis, we demonstrated that GDF-9B and GDF-9 mRNAs are co-localized in the oocyte. We also showed that GDF-9B and GDF-9 genes are co-ordinately expressed during follicular development.

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PMID: 9858711 [PubMed - indexed for MEDLINE]

☐ 31: Arch Oral Biol 1998 Sep;43(9):745-51

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Transforming growth factor-beta superfamily members expressed in rat incisor pulp.

Nakashima M, Toyono T, Murakami T, Akamine A.

Department of Operative Dentistry and Endodontology, Faculty of Dentistry, University of Fukuoka, Japan.

The transforming growth factor (TGF)-beta superfamily comprises more than 30 structurally related genes that have been implicated in embryonic induction and tooth morphogenesis. Different superfamily members may have distinct regulatory roles in tooth development and maintenance. Degenerate primer sets derived from the conserved carboxy terminal region of the TGF-beta superfamily were used in a polymerase chain reaction (PCR) with poly(A)⁺ RNA from the rat incisor pulp as a template. TGF-beta superfamily members expressed in the pulp with known potential to differentiate into odontoblasts and to form dentine were identified. Nucleotide sequence analysis of the amplified cDNAs identified those encoding activin-betaB; bone morphogenetic protein (BMP)-2, -4, -7 and -8; growth/differentiation factor (GDF)-5 and -6; and glial cell line-derived neurotrophic factor. In addition, Northern blot analysis detected TGF-beta1, -beta2 and -beta3; activin-betaA; BMP-6 and GDF-7 transcripts in the pulp. Coordinated expression of TGF-beta superfamily members in the pulp may be critical in tooth development and repair.

PMID: 9783830 [PubMed - indexed for MEDLINE]

☐ 32: Growth Factors 1998;15(2):81-94

Related

Characterization of growth factor responsiveness and alterations in growth factor homeostasis involved in the tumorigenic conversion of mouse oval cells.

Isfort RJ, Cody DB, Richards WG, Yoder BK, Wilkinson JE, Woychik W.

Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45206, USA.

Five mouse oval cell lines were investigated in regards to their growth and growth factor (GDF) responsiveness and to changes in their GDF responsiveness following tumorigenic conversion. In all 59 GDFs and 11 comitogens were evaluated for responsiveness, depending on the mouse oval cell line under study, observed

oval cell GDF responsiveness during tumorigenic conversion revealed that variants displayed alterations in GDF responsiveness which correlated with tumorigenicity. In addition, analysis of autocrine/paracrine growth factor production demonstrates that most tumorigenic variants produce growth factors. These demonstrate for the first time that (1) mouse oval cells respond to a wide variety of GDFs including various members of the interleukin, chemokine, stem cell factor, FGF, PDGF, TGF-beta, VEGF, insulin, CSF, TNF, HGF, and IFN growth factor and differentiation factor families in addition to multiple mitogens and (2) during tumorigenic conversion mouse oval cells undergo alterations which result in alterations in GDF responsiveness and the autocrine/paracrine production of GDFs.

PMID: 9505165 [PubMed - indexed for MEDLINE]

□ 33: Pharmazie 1998 Jan;53(1):51-7

Relate

Effects of growth factors on the proliferation of human keratin fibroblasts in vitro.

Kim DS, Korting HC, Schafer-Korting M.

Abteilung für Pharmakologie und Toxikologie, Freie Universität Berlin, Germany

Growth/differentiation factor-5 (GDF-5) is a new member of the transforming growth factor-beta (TGF-beta) superfamily of multifunctional peptide growth factors that is thought to mediate many key events in cell growth and development. The effects of GDF-5 on the proliferation of human keratinocytes and fibroblasts compared with desoximetasone and calcipotriol have been investigated. The proliferation rate was determined by a hemocytometer assay and the incorporation of [3H]-thymidine. Moreover, cell cycle analysis was performed and the influence on interleukin-1 alpha (IL-1 alpha) production in keratinocytes was measured by enzyme-linked immunosorbent assay (ELISA). GDF-5 showed its pronounced proinflammatory effect. In keratinocytes, GDF-5 stimulated proliferation to a minor extent. The drug already proved to be effective at very low concentrations (0.1 ng/ml). Growth stimulatory effects with EGF have been observed only in keratinocyte basal medium (KBM), but not in keratinocyte growth medium (KGM). TGF-beta 1 markedly inhibited the proliferation of keratinocytes at concentrations > 1 ng/ml. Calcipotriol and desoximetasone also showed a dose-dependent cell growth inhibition in epidermal cell cultures. IL-1 alpha synthesis was greatly suppressed by calcipotriol 10⁻⁸-10⁻⁶ M. EGF at 10 ng/ml, in contrast, stimulated IL-1 alpha production. Neither GDF-5 nor TGF-beta 1 had a significant effect on IL-1 alpha production in keratinocyte monolayer cultures. In fibroblasts, GDF-5 induced very weak antiproliferative effects. Calcipotriol and desoximetasone inhibited cell growth in fibroblast cultures whereas proliferation and DNA synthesis were strongly stimulated by 1 ng/ml EGF. There was, however, a contradictory effect of TGF-beta 1 on fibroblasts. Whereas TGF-beta 1 increased proliferation in number determination and in the thymidine incorporation assay, MTT assay showed slight antiproliferative effects. Due to these controversial results, in addition

analysis was employed. TGF-beta 1 led to an increased S phase, which indicates stimulation of cell division. The different results obtained with the MTT test suggest that TGF-beta 1 may stimulate cell division of fibroblasts not only by increasing but also by shortening the G1 phase of the cell cycle.

PMID: 9476258 [PubMed - indexed for MEDLINE]

□ 34: J Cell Sci 1997 Dec;110 (Pt 24):3117-29

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The combination of epidermal growth factor and transforming factor-beta induces novel phenotypic changes in mouse liver stem cell lines.

Isfort RJ, Cody DB, Stuard SB, Randall CJ, Miller C, Ridder GM, Doerflinger WG, Richards WG, Yoder BK, Wilkinson JE, Woychik RP.

Proctor & Gamble Pharmaceuticals, Health Care Research Center, Mason, Ohio 45040, USA.

Mouse liver stem cell (oval cell) lines were investigated in order to determine which two families of growth and differentiation factors (GDFs), epidermal growth factor (EGF) family and transforming growth factor beta (TGF-beta) family, regulate stem cell regeneration. EGF family members, including EGF, amphiregulin, betacellulin, and transforming growth factor alpha, were mitogenic for oval cell lines, while TGF-beta family members, including TGF-beta1, TGF-beta2 and TGF-beta3, inhibited mitogenesis and induced apoptosis in oval cell lines. Surprisingly, combination of EGF family members and TGF-beta family members resulted in proliferation and survival but instead in a novel cellular response, cellular differentiation and morphological differentiation in Matrigel. Analysis of the transduction pathways activated by exposure of oval cell lines to either EGF family members, or TGF-beta indicated that novel combinations of intracellular signals following stimulation of the cells with the combination of EGF+TGF-beta. These results reveal that the dynamics of synergistic GDF action following tissue injury and regeneration results in a new level of complexity not obvious from the study of individual GDFs.

PMID: 9365282 [PubMed - indexed for MEDLINE]

□ 35: J Neurosci Res 1998 Jan 15;51(2):139-46

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Bone morphogenetic proteins and their receptors: potential functions in the brain.

Ebendal T, Bengtsson H, Soderstrom S.

Department of Developmental Neuroscience, Uppsala University, Sweden.
Ted.Ebendal@mun.uu.se

Transforming growth factors-beta (TGF-betas), activins, and bone morphogenetic proteins (BMPs) comprise an evolutionarily well-conserved group of proteins involved in a number of cell differentiation, cell growth, and morphogenetic processes during development. The superfamily of TGFbeta-related genes include over 25 members in mammals several of which are expressed in the growing nervous system and perform important functions in regionalizing the early CNS. Cultured nerve cells show specific responses to these factors. Recent developments have revealed that TGFbeta and BMPs selectively signal to the responding cells via different hetero-oligomeric complexes of type I and type II serine/threonine kinase receptors. The adult brain exhibits specific expression patterns of some of these receptors suggesting functions not only during development but also in the mature brain. In particular, the brain is expressing high levels of bone morphogenetic protein receptor type II (BMPRII), activin receptor type I (ActRI), and activin receptor type IIA (ActRII). This indicates that osteogenic protein-1 (OP-1/BMP-7), BMP-2, and BMP-4 as well as activins may serve functions for brain neurons. Expression of the receptors overlaps in populations of neurons and has been shown to be regulated by both TGFbeta and BMPs. This suggests that brain neurons may use receptors BMPRII and ActRI to transduce the presence of BMPs. This may form a system parallel to the neurotrophin Trk kinase receptors regulating neuroplasticity and brain repair. The presence of BMPs in the brain is not well studied, but preliminary in situ data indicate that the BMP growth/differentiation factor (GDF)-1 and GDF-10 are distinctly but differentially expressed at high levels in neurons expressing BMPRII and ActRI. The receptors mediating responses to these two GDFs remain, however, to be defined. Further data show that the signal from the activated type I serine/threonine kinase receptor is directly transduced to the nucleus by Smad proteins that become incorporated into transcriptional complexes. Preliminary in situ hybridization observations demonstrate the existence of different Smad mRNAs. It is concluded that BMPs and their signaling systems may comprise a novel pathway for control of neural activity and of pharmacological interventions rescuing brain neurons.

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PMID: 9469567 [PubMed - indexed for MEDLINE]

36: J Clin Invest 1997 Jul 15;100(2):321-30

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Ectopic induction of tendon and ligament in rats by growth and differentiation factors 5, 6, and 7, members of the TGF-beta gene family

Wolfman NM, Hattersley G, Cox K, Celeste AJ, Nelson R, Yamaji N, DiBlasio-Smith E, Nove J, Song JJ, Wozney JM, Rosen V.

Genetics Institute, Inc., Cambridge, Massachusetts 02140, USA.

Little is known about the regulatory signals involved in tendon and ligament and this lack of understanding has hindered attempts to develop biologically therapies for tendon and ligament repair. Here we report that growth and differentiation factors (GDFs) 5, 6, and 7, members of the TGF-beta gene superfamily that related to the bone morphogenetic proteins, induce neotendon/ligament formation implanted at ectopic sites in vivo. Analysis of tissue induced by GDF-5, 6, and 7 containing implants by currently available morphological and molecular criteria to characterize tendon and ligament, adds further evidence to the idea that these as signaling molecules during embryonic tendon/ligament formation. In addition, comparative in situ localizations of the GDF-5, 6, and 7 mRNAs suggest that these molecules are important regulatory components of synovial joint morphogenesis.

PMID: 9218508 [PubMed - indexed for MEDLINE]

☐ 37: Nature 1997 May 1;387(6628):83-90 Related Articles, Nucleotide, OMIM, Protein

Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member.

McPherron AC, Lawler AM, Lee SJ.

Department of Molecular Biology and Genetics, Johns Hopkins University Medicine, Baltimore, Maryland 21205, USA.

The transforming growth factor-beta (TGF-beta) superfamily encompasses a family of growth and differentiation factors playing important roles in regulating embryonic development and in maintaining tissue homeostasis in adult animals. Using polymerase chain reaction, we have identified a new murine TGF-beta family member, growth/differentiation factor-8 (GDF-8), which is expressed specifically in embryonic and adult skeletal muscle. During early stages of embryogenesis, GDF-8 expression is restricted to the myotome compartment of developing somites. At later stages in adult animals, GDF-8 is expressed in many different muscles throughout the body. To determine the biological function of GDF-8, we disrupted the GDF-8 gene by homologous recombination targeting in mice. GDF-8 null animals are significantly larger than wild-type animals and show a large and widespread increase in skeletal muscle mass. Individual null mutant animals weigh 2-3 times more than those of wild-type animals, and this increase in mass appears to result from a combination of muscle cell hyperplasia and hypertrophy. These results suggest that GDF-8 functions specifically as a negative regulator of muscle growth.

PMID: 9139826 [PubMed - indexed for MEDLINE]

☐ 38: Kokubyo Gakkai Zasshi 1997 Mar;64(1):24-37

Related

[Identification of receptors for bone morphogenetic proteins].

[Article in Japanese]

Nishitoh H.

Second Department of Oral and Maxillofacial Surgery, Faculty of Dentistry Medical and Dental University.

Bone morphogenetic protein (BMP)-7/osteogenic protein (OP)-1 and growth/differentiation factor (GDF)-5 are members of the BMP family. BM their effects through binding to two different types of serine/threonine kinase type I and type II. Here we investigated the binding and signaling properties of BMP-7/OP-1 and GDF-5 through type I and type II receptors. BMP-7/OP-1 was found to bind to Activin receptor-like kinase (ALK)-1 as well as ALK-3/BMPR-IA in ATDC-14 cells. When ALK-1 or ALK-3/BMPR-IA was stably transfected into mink lung epithelial cells, ALK-1 and ALK-3/BMPR-IA mediated signals for BMP-7/OP-1 with heterogeneous signaling specificities. GDF-5 bound to ALK-6/BMPR-IB and BMP type II receptor (BMPR-II) but not to ALK-3/BMPR-IA in ROB-C26 cells. Analysis using a pull-down assay revealed that GDF-5 bound to ALK-6/BMPR-IB, but not to the other type I receptors when expressed alone. When COS-1 cells were transfected with type II receptors, GDF-5 bound to Activin type II receptor (ActR-II) and type IIB receptors as well as BMPR-II but not to TGF-beta type II receptor. In the presence of type II receptors, GDF-5 bound to different sets of type I receptors, but the binding was most efficient with ALK-6/BMPR-IB compared to the other type I receptors. Moreover, GDF-5 transduced a signal efficiently by ALK-6/BMPR-IB in the presence of BMPR-II or ActR-II.

PMID: 9125848 [PubMed - indexed for MEDLINE]

39: Nat Genet 1996 Mar;12(3):315-7

Related Articles, OMIM

A human chondrodysplasia due to a mutation in a TGF-beta signal transducer member.**Thomas JT, Lin K, Nandedkar M, Camargo M, Cervenka J, Luyten FJ**

Bone Research Branch, National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland 20892, USA.

The TGF-beta superfamily comprises a number of functionally diverse growth factors/signalling molecules (1) which elicit their response upon binding to serine/threonine kinase receptors (2). We recently reported the isolation and characterization of two new members of the family, designated cartilage-derived morphogenetic protein (CDMP) 1 and 2 (ref. 3) which are closely related to the sub-family of bone morphogenetic proteins. CDMP-1 is predominantly expressed at sites of skeletal morphogenesis (3), and we now show that a mutation in hCDMP-1 is associated with a recessive human chondrodysplasia (acromesomelic chondrodysplasia, Hunt

type (4,5)). The disorder, characterized by skeletal abnormalities restricted to hand and limb joints, is phenotypically similar to murine brachypodism (bp) which has mutations in growth/differentiation factor-5 (Gdf-5) (6), the mouse homolog of hCDMP-1. Affected individuals are homozygous for a 22-bp (tandem-duplication) frameshift mutation in the mature region of CDMP-1. The resulting phenotype provides direct evidence for the involvement of CDMP-1 in human skeletal development. This represents the first human disorder attributable to a mutation in a TGF-beta family member.

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Relate

Divide, accumulate, differentiate: cell condensation in skeletal development revisited.

Hall BK, Miyake T.

Department of Biology, Dalhousie University, Halifax, Nova Scotia, Canada

Cell condensation is a pivotal stage in skeletal development. Although prechondrocondensations normally exist for some 12 h, duration can vary. Variation is between condensations for different cartilages (Meckel's vs. elastic ear cartilage) within a single condensation from which more than one skeletal element will arise--the three components of the single first arch chondrogenic condensation. Until now, how duration of the condensation phase is established--how the condensation entered and exited during cell differentiation--remains a major area for future study. During chondrogenesis, cell-specific products such as collagen types II and III and cartilage proteoglycan appear concomitant with condensation. Therefore, during chondrogenesis, condensation precedes commitment of cells as prechondrocytes. However, during osteogenesis, differentiation of preosteoblasts precedes condensation. Therefore, during osteogenesis, condensation amplifies the number of committed osteogenic cells. Further comparative analysis of skeletogenesis should promote a more rigorous understanding of cell commitment, when differentiation is in progress and commitment and differentiation are measured and the relationship of condensation to onset of differentiation. Current knowledge of molecules characteristic of chondrogenesis has focused attention on extracellular matrix and cell surface components on the one hand and on growth factors, homeobox genes and transcription factors on the other. We have drawn together the molecular data for pre-chondrogenic condensations in different forms in Figure 2. Three major phases of chondrogenesis are identified: (a) cell-mesenchymal interactions that precede condensation, (b) condensation itself and (c) differentiation. Although we label the third phase differentiation, it is important to recognize that phases a and b also constitute aspects of chondroblast cell differentiation (see Dunlop and Hall, 1995 for a discussion of this point). The pre-condensation phase is characterized by expression of Hox genes, growth factors (TGF-beta and BMPs), cell surface proteoglycan receptor, syndecan-1. Expression of Msx-1 and Msx-2 factors and syndecan continues into the condensation phase. Other molecules, including versican, syndecan-3 and tenascin, present in low concentrations before con-

are up-regulated during condensation. Yet other molecules--Hox genes, transcription factors, growth factors (activin, BMP-4 and -5, GDF-5), cell adhesion molecules, proteoglycans--are only expressed during the condensation phase, while the factor Pax-1, fibronectin, hyaluronan and hyaladherin are expressed both during condensation. During condensation mRNAs for collagen types II and IX and protein of cartilage proteoglycan are up-regulated. Late in condensation and thereafter, the protein products of these genes accumulate as chondroblasts (see Fig. 2 for details). Not all the molecules present before, during or after can be placed into causal sequences. Some however can. In Figure 3 we summarize causal sequences discussed in this paper as they relate to initiation of condensation to transit from condensation to overt differentiation during chondrogenesis. Condensations form following activation of at least three pathways: (1) Initiation of epithelial-mesenchymal interactions by tenascin, BMP-2, TGF beta-1 and N-CAM. (2) Up-regulation of N-CAM by activin. (3) Up-regulation of fibronectin by further enhancing N-CAM accumulation (Fig. 3). It is by these three pathways that condensations are initiated and grow. Transition from condensation to overt differentiation is under both positive and negative control (Fig. 3). Syndecan-1 and fibronectin and so blocks N-CAM accumulation, preventing accumulation of cell

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